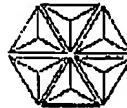


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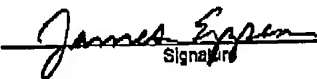
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE APPLICATION OF Boy et al.

APPLICATION NO: 10/731,854

FILED: 12/9/2003

FOR: 2-Aryl thiazole derivatives as KCNQ modulators

EXAMINER: Patricia Morris

ART UNIT: 1625

Director of Technology Center 1600

P.O. Box 1450

Alexandria, VA 22313-1450

Petition from requirement for restriction under 37 CFR 1.144

Sir:

We received the office action dated March 23, 2005 which made a restriction requirement final. The applicants now respectfully request the Technology Center Director to review and reconsider the restriction requirement. The applicants request the director to reinstate claims 3, 4, and 9 and have claims 1-11 examined throughout their full scope.

The applicants have preserved their right to petition. In the first office action, the examiner required election of one of three grouped inventions and election of a species within the elected group. In the first reply, the applicants elected group I with traverse, elected a species, and requested reconsideration of the requirement under 37 CFR 1.143. In the second office action, the examiner examined the elected group, but limited the scope of the claim terms examined. In the second reply, the applicants traversed this further intra-claim restriction and requested reconsideration of the restriction under 37 CFR 1.143. In the current office action, the examiner made the restriction requirement final.

The applicants have complied with all requirements for election, traversal, and requests for reconsideration and have preserved their right to petition the restriction requirement.

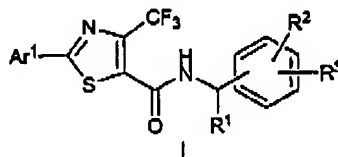
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Status of the claims. Claims 1 and 3-17 are pending. Claim 2 has been cancelled. Claims 3, 4, 9 and 12-27 were withdrawn from consideration by the examiner. Claims 1, 5-8, and 10-11 are objected to for containing non-elected matter.

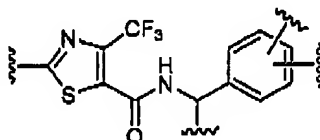
The applicants' request is limited to the Markush variables. The examiner required, in effect, three restrictions. The applicants are only concerned with the last of these restrictions. In the first office action, the examiner required both (1) an inter-claim restriction between composition of matter claims and method of use claims and (2) an intra-claim restriction limiting compounds to those of structure I (shown below).



In the next office action, the examiner examined the application with respect to structure I, but did not examine the full scope of the claims. Instead, the examiner restricted the scope of the variables to that of her own choosing and deemed the examined subject matter allowable (see current office action pp. 2-3 included as appendix 1). The applicants are traversing this restriction of the scope of the variables.

In the current and pending office action, the examiner made final the curtailed claim scope and objected to the claims for containing non-elected matter. Because the claims are objected to and not rejected, the applicants believe this petition is the proper recourse for having the full scope of the claims examined.

For Markush claims, the PTO has adopted the guidelines of *In re Harnisch* and should examine the full scope of a claim so long as the claimed compounds share a common utility and a substantial structural feature. *In re Harnisch*, 631 F.2d 716 (CCPA, 1980). The applicants have described 122 examples (see specification pp. 24-31 included as Appendix 2) which show that there is a class of KCNQ modulators which share a substantial structural feature (shown below) and should be examined in their entirety.



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Furthermore, variable substituents which create independent and distinct inventions do not detract from unity of invention so long as the compounds as a whole can be considered as belonging to the same class. As *Harnisch* further states: "Where a Markush expression is applied only to a portion of a chemical compound, the propriety of the grouping is determined by a consideration of the compound as a whole, and does not depend on there being a community of properties in the members of the Markush expression." [emphasis added]

For this reason, the applicants believe the examiner improperly restricted the scope of the Markush variables of the claimed compounds. The applicants believe they are entitled to the full scope of coverage for the class of compounds they invented and that the invention should not be fragmented into applications that deliver less than that full scope.

The applicants respectfully request the director to reinstate claims 3, 4, and 9 and have claims 1-11 examined throughout their full scope.

The applicants believe the application is allowable and respectfully request favorable reconsideration. If any issues remain regarding the allowance of this application, the director or the examiner is respectfully invited to contact the applicants' agent, James Epperson, by phone (203-677-6974), fax (203-677-6900), or e-mail (james.epperson@bms.com).

Respectfully submitted,

Date: 4/5/2005
Bristol-Myers Squibb Company
Patent Department
P.O. Box 4000
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James Epperson
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Agent for Applicants
Reg. No. 52,867
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Art Unit: 1625

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DETAILED ACTION

Claims 1, 5-8, 10 and 11 are under consideration in this application.

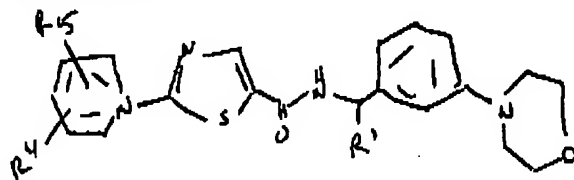
Claims 3, 4, 9 and 12-17 remain held withdrawn from consideration as being drawn to nonelected subject matter 37 CFR 1.142(b).


Election/Restrictions

The requirement is still deemed sound and proper and is therefore maintained for the reasons clearly set forth in the record and is hereby made FINAL. Applicants have already been given the elected species and was expanded to give a reasonable genus. Further, applicants have failed to advance any cogent reasons as to why the compounds are not patentably distinct. Either it is one invention or it is not. Applicants cannot have it both ways. If one were to hold unity of invention, then one reference will be a reference for the entire genus.

It is too burdensome for the examiner to search all of the previously noted searches in their respective, completely divergent, areas for the non-elected subject matter, as well, in the limited time provided to search one invention.

Again, this application has been examined with regard to the elected compound and expanded to include a genus wherein





R² is -NR⁶R⁷ wherein R⁶ and R⁷ taken with the nitrogen form a morpholine ring, R⁴ is halogen, C₁₋₆alkyl, C₁₋₆alkoxy, -NR⁶R⁷, -(CH₂)₁₋₄NR⁶R⁷, O(CH₂)₂₋₃NR⁶R⁷ or , R⁶ is

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hydrogen, C₁₋₆alkyl, -C(=NH)NH₂,  or , R⁷ is hydrogen or C₁₋₆alkyl and R⁵ as set forth in Claim 1, exclusively.

Claims 12-17 will NOT be rejoined because they are not readable on the elected compounds. Further, claims 12-17 fail to meet the requirements set forth in 35 U.S.C. 101 and 112.

Allowable Subject Matter

Claim 1 is objected to as containing nonelected subject matter. The objection may be overcome by limiting the claim to the subject matter indicated as being examinable, supra. A claim so limited would appear allowable.

Claims 5-8, 10 and 11 presented in independent form or made dependent on an allowable claim, would appear allowable, otherwise it is objected to as being dependent on a nonallowed claim.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia L. Morris whose telephone number is (571) 272-0688.

The examiner can normally be reached on Mondays through Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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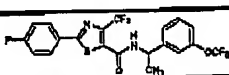
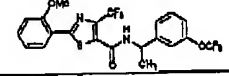
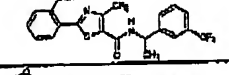
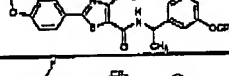
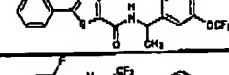
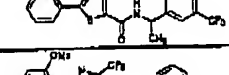
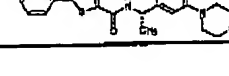
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For data analysis, the amplitude of the average of the negative controls was subtracted from all wells. The amplitudes of the test compounds were then compared to the value of four standard deviations of the negative control wells. The lowest concentration of a test compound sufficient to generate a signal amplitude greater than or equal to four standard deviations from the amplitude of the negative controls was defined as the minimal active concentration.

For generating EC_{50} values, compounds were serially diluted in 1:3 volume increments to produce a 10 point concentration series. EC_{50} values were calculated by fitting the resulting amplitudes to a single-site logistic equation. EC_{50} was defined as the concentration of test compound required to yield 50% of the maximal response. Maximal response (Maximal opening) was the largest signal amplitude divided by the negative control amplitude generated by any concentration of a test compound.

Table 1 describes the effect of representative Formula I compounds on KCNQ channels.

Table 1.

Example	Structure	Min. conc. response (μM)	EC_{50} (μM)
17		0.3	+++
18		0.3	+++
19		3	+++
20		0.3	+
21		0.3	+++
22		0.3	+++
23		3	++

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Example	Structure	Min. conc. response (μ M)	EC ₅₀ (μ M)
24		3	++
25		3	+
26		3	++
27		3	+
28		10	+
29		3	++
30		3	++
31		3	+
32		0.3	+++
33		3	++
34		0.3	+++
35		0.3	++
36		10	+
37		3	+
38		30	+
39		10	+
40		30	+
41		10	++
42		10	++

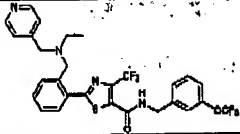
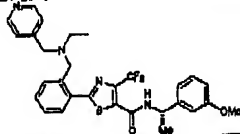
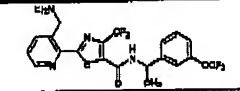
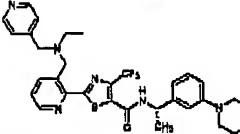
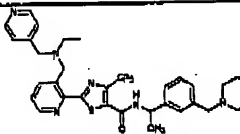
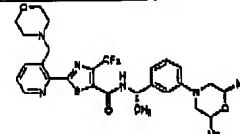
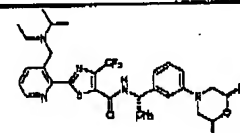
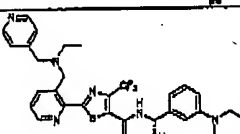
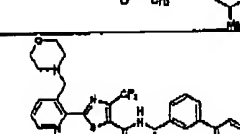
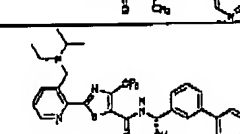
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Example	Structure	Min. conc. response (μ M)	EC ₅₀ (μ M)
43		3	++
44		3	++
45		3	+
46		10	+
47		3	+
48		3	++
49		0.3	++
50		0.3	++
51		0.3	++
52		3	++
53		3	+
54		0.3	+
55		0.3	+
56		0.3	++
57		0.3	++
58		30	++

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Example	Structure	Min. conc. response (μ M)	EC ₅₀ (μ M)
59		3	++
60		0.3	++
61		30	++
62		3	++
63		30	++
64		10	++
65		10	++
66		3	++
67		30	++
68		30	+

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Example	Structure	Min. conc. response (μ M)	EC ₅₀ (μ M)
69		3	++
70		3	++
71		30	++
72		3	++
73		0.3	++
74		3	+
75		30	++
76		10	++
77		0.3	+
78		3	++
79		3	++
80		3	+
81		30	++
82		0.3	++
83		0.3	na

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Example	Structure	Min. conc. response (μ M)	EC ₅₀ (μ M)
84		30	na
85		30	na
86		3	na
87		0.3	na
88		30	na
89		30	na
90		10	na
91		30	na
92		3	na
93		10	na
94		30	na
95		0.3	na
96		3	na
97		10	na
98		3	na
99		3	na
100		30	na

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Example	Structure	Min. conc. response (μ M)	EC ₅₀ (μ M)
101		3	na
102		0.3	na
103		0.3	na
104		10	na
105		30	na
106		10	na
107		30	na
108		0.3	na
109		3	na
110		3	na
111		0.3	na
112		30	na
113		0.3	na

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Example	Structure	Min. conc. response (μ M)	EC ₅₀ (μ M)
114		3	na
115		3	na
116		3	na
117		0.3	na
118		10	na
119		3	na
120		0.3	+++
121		3	+
122		30	na
123		3	na
124		3	na

EC₅₀ values: +++ = <50 nM, ++ = 50-1000 nM, + = 1000-20000 nM.

KCNQ Patch-clamp. Whole-cell patch-clamp recordings were made from an HEK 293 stable cell line expressing mKCNQ2 channels, maintained in culture for 1-

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